Sex Differences in Outcome After Endovascular Stroke Therapy for Acute Ischemic Stroke

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Background and Purpose—We determined the effect of sex on outcome after endovascular stroke thrombectomy in acute ischemic stroke, including lifelong disability outcomes.

Methods—We analyzed patients treated with the Solitaire stent retriever in the combined SWIFT (Solitaire FR With the Intention for Thrombectomy), STAR (Solitaire FR Thrombectomy for Acute Revascularization), and SWIFT PRIME (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment) cohorts. Ordinal and logistic regression were used to examine known factors influencing outcome after endovascular stroke thrombectomy and study the effect of sex on the association between these factors and outcomes, including age and time to reperfusion. Years of optimal life after thrombectomy were defined as disability-adjusted life years and calculated by projecting disability through adjusted poststroke life expectancy by sex.

Results—Among 389 patients treated with endovascular stroke thrombectomy, 55% were females, and median National Institutes of Health Stroke Scale was 17 (interquartile range, 8–28). There were no differences between females versus males in presenting deficit severity (National Institutes of Health Stroke Scale score, 17 versus 17, P=0.21), occlusion location (69% versus 64% M1, P=0.62), presenting infarct extent (Alberta Stroke Program Early CT Score 8 versus 8, P=0.24), rate of substantial reperfusion (Thrombolysis in Cerebral Infarction 2b/3, 87% versus 83%, P=0.37), onset to reperfusion time (294 versus 302 minutes, P=0.46). Despite older ages (69 versus 64, P<0.001) and higher rate of atrial fibrillation (45% versus 30%, P=0.002) for females compared with males, adjusted rates of functional independence at 90 days were similar (odds ratio, 1.0; 95% CI, 0.6–1.6). After adjusting for age at presentation and stroke severity, females had more years of optimal life (disability-adjusted life year) after endovascular stroke thrombectomy, 10.6 versus 8.5 years (P<0.001).

Conclusions—Despite greater age and higher rate of atrial fibrillation, females experienced comparable functional outcomes and greater years of optimal life after intervention compared with males. **(*Stroke*. 2019;50:2420-2427. DOI: 10.1161/STROKEAHA.118.023867.)**

Key Words: cerebrovascular stroke ■ life expectancy ■ reperfusion ■ sex ■ thrombectomy

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Acute ischemic stroke (AIS) appears to affect females differently than males.[1] For stroke treatments, intravenous and intra-arterial thrombolysis may have differing recanalization effectiveness by sex.[2–8] In addition, a number of studies have suggested worse outcomes from AIS for females compared with males,[1,5,9,10] including worse functional outcomes for females despite adjustment for age, prestroke modified Rankin Scale (mRS), and stroke severity.[11,12] However, other studies have suggested that these differences may be secondary to differing presentations in females compared with males, including later age of onset, differences in stroke etiology, and greater prestroke disability.[13–15]

In recent years, endovascular stroke thrombectomy (EST) has demonstrated dramatic improvements in outcomes for eligible patients with large vessel occlusion AIS. The rates of

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substantial reperfusion and effect on 90-day disability are far greater than those observed in the thrombolysis-only era, and as such, the influence of sex on these outcomes may be different. A post hoc analysis of the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) suggested greater 90-day mortality and more adverse events after EST in females compared with males, though other series, including a large meta-analysis, have shown no differences.[16–18] However, because of differences in age of onset and poststroke mortality between the sexes, 90-day outcomes may be insufficient to characterize the differences in EST outcome on poststroke disability, as they do not account for poststroke lifetime disability, which could be substantially different between males and females.[14]

In this study, we aimed to perform a comprehensive evaluation of the effect of sex on outcome after EST in AIS. To do so, we studied the differential effect of factors known to influence outcomes after EST in females versus males, including age, onset to reperfusion time (OTR), collateral grade, and final infarct volume. We then determined disability-adjusted life years (DALYs), integrating disability and mortality after disease to quantify the disease burden and treatment benefits to provide a thorough study of the effect of sex on outcomes in EST.[19,20]

Methods

Study Design and Participants

The authors declare that all supporting data are available within the article and its online-only Data Supplement.

We performed a pooled, post hoc, exploratory analysis of the SWIFT (Solitaire FR With the Intention for Thrombectomy), STAR (Solitaire FR Thrombectomy for Acute Revascularization), and SWIFT PRIME (Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment) clinical trials. Patients were included if they were treated with EST with the Solitaire FR stent-retriever within the inclusion criteria for these studies. Details of these trials have been published previously and are briefly summarized here. SWIFT was a multicenter, randomized, prospective, parallel-group trial with blinded primary end point ascertainment.[21] The STAR trial was an international, prospective, multicenter, single-arm study.[22] SWIFT PRIME was a multicenter, randomized, prospective, dual-arm study with blinded primary and secondary end point assessment.[23] Briefly, for all 3 studies, patients were eligible if they had AIS with moderate to severe neurological deficits, harbored angiographically confirmed occlusions of proximal cerebral arteries, and were treatable by thrombectomy within 8 hours of stroke symptom onset (6 hours for SWIFT PRIME). Key inclusion criteria included age (22–85 years in SWIFT, 18–85 years in STAR, 18–80 years in SWIFT PRIME) and National Institutes of Health Stroke Scale (NIHSS) score 8 to 30. Whereas SWIFT and STAR required ineligibility for or failure to respond to IV-tPA (intravenous tissue-type plasminogen activator) with documented occlusion of an anterior intracranial artery, SWIFT PRIME required that all enrolled patients have received IV-tPA within 4.5 hours of symptom onset (within 3 hours in the United States). Key exclusion criteria included uncontrolled hypertension, serious sensitivity to radiographic contrast agents, and computed tomography (CT) or magnetic resonance imaging evidence of intracranial hemorrhage or major ischemic infarction (acute ischemic change in more than a third of the middle cerebral artery territory or >100 mL of tissue in other territories). The studies were approved by the appropriate national regulatory bodies and by the ethics committee at each center. All patients or their legally authorized representatives provided signed, informed consent.

Procedures

In the SWIFT trial, once enrolled, patients were treated with the Solitaire stent-retriever device (roll-in phase) or randomized to treatment with the Solitaire stent-retriever device or the Merci device (randomized phase). All patients in the STAR study were treated with the Solitaire device. In SWIFT PRIME, patients were randomized to either receiving treatment with the Solitaire stent-retriever device (with tPA) or medical therapy alone. In this analysis, we included only patients treated with the Solitaire device for anterior circulation occlusions (internal carotid artery or middle cerebral artery). Successful reperfusion in SWIFT was defined as TIMI (Thrombolysis in Myocardial Infarction) 2 or 3 flow in all treatable vessels.[21] Successful reperfusion in STAR and SWIFT PRIME was defined as Thrombolysis in Cerebral Infarction (TICI) 2b or 3.[22,23] For the purpose of this analysis and to be consistent with the other 2 studies, angiograms in the SWIFT study were rescored on the TICI scale. All imaging data were adjudicated by blinded independent core labs. Thus, successful reperfusion throughout this study has been defined as TICI 2b or 3. OTR was defined as the time from when the patient was last known to be well until the visualization of successful reperfusion as defined above in all treatable vessels. Global disability at 3 months was assessed with the 7-level mRS in all 3 studies. Intracranial hemorrhage was graded by as hemorrhagic infarct (type 1 or 2) or parenchymal hematoma (type 1 or 2).[24] Angiographic collateral scales were graded by the Society of Interventional Radiology/American Society of Intervention and Therapeutic Neuroradiology (SIR/ASITN) grading scale, which assigns 5 possible scores ranging from no collateral flow to complete and rapid flow to the ischemic territory.

DALY Calculations

The primary outcome of this study was differences in DALYs for females versus males after EST. DALY outcomes were defined as DALYs gained to represent life expectancy adjusted for disability, and as such, an increase in DALYs indicates an improved outcome. DALYs gained was calculated for each patient in the study individually by estimating poststroke life expectancy and adjusting that life expectancy by disability weightings related to their 90-day mRS outcomes.

Age-specific life expectancy given observed 90-day poststroke disability outcomes were determined from 2 European studies, as described previously.[25] Full healthy life expectancy (age-specific life expectancy without stroke) was derived from the 2004 US life table for sex and race.[26] Disability weightings for the ordinal mRS were obtained using the person trade-off procedure developed by the World Health Organization Global Burden of Disease Project ranging from 0 (normal) to 1 (dead) and utilized to develop mRS-specific mortality hazard ratios as previously described.[27] As such, we modeled DALYs gained (years of optimal life)=full healthy life expectancy−(life expectancy of normal age of stroke X mRS-specific disability weight) for males. For DALYs in females, mortality rates for females relative to males after stroke adjusted for age, stroke severity, atrial fibrillation, and prestroke disability were obtained from a population-based study of nearly 17 000 participants across 4 continents and 27 years. In this study, females were found to have lower poststroke mortality after these adjustments compared with males.[14] As such, for poststroke life expectancy in females, the lower mortality rate (a fixed multiplier of 0.76) was combined with a model of males by dividing life expectancy of normal age of stroke X mRS-specific disability weight with the lower rate. Then in sensitivity analysis, poststroke life expectancy for males and females were kept the same, excluding the lower mortality for females.

DALYs were then summed up after adjustment for age and stroke severity, prestroke mRS, atrial fibrillation, smoking status, and use of IV-tPA. Results are presented in both unadjusted results (not accounting for age of onset, stroke severity, prestroke mRS, atrial fibrillation, smoking status, use of IV-tPA, and poststroke mortality differences), as well as adjusted results, which do account for these differences.

Statistical Analysis

Key statistical analyses, including the primary end point analysis, were validated by an independent external statistician. For unadjusted (eg, baseline) metrics, analyses of continuous variables were calculated by *t* test (when mean is reported) or Wilcoxon test (when median is reported). Analyses of discrete variables were conducted using Fisher exact test.

For analysis of DALY values, polynomial regression was used, adjusted for age and NIHSS at baseline. Model fit was tested using quadratic and interaction terms for the various predictors incorporated into generalized linear models and significant higher-order terms were included in modeling; these included quadratic terms for age and interaction terms for age by NIHSS and age by sex. *P* values were derived via ANCOVA, using type III errors.

In comparisons of 90-day neurological outcomes, good neurological outcome was defined as mRS 0 to 2 and adjusted for age, baseline NIHSS, atrial fibrillation, and premorbid mRS using multivariate logistic regression. We then examined the differential effect of age and OTR on EST outcomes in females versus males using multivariate logistic regression, with a dichotomous end point (mRS, 0–2). These analyses were adjusted for baseline NIHSS,[28–33] target occlusion location,[18,34,35] Alberta Stroke Program Early CT Score (ASPECTS),[36] baseline serum glucose,[30,37] prestroke mRS,[28,31,32,37] atrial fibrillation,[28–33,37–41] smoking status,[28,31,32,37] atrial fibrillation,[28–33,37–41] use of IV-tPA,[29,30,33,41] year of age by sex (AGE×SEX interaction term)[14] and age.[28–33,37–41] Of note, in the logistic regression examining the differential effect of age on EST outcomes in females versus males, all the above covariates were included except age and AGE×SEX interaction term. In addition, adjusted ordinal logistic regression was used to model the effect of OTR on 90-day outcomes across the 7-level entire distribution of mRS and adjusted for same variables. In the multivariate analyses on the differential effect of age and OTR on EST outcomes in females versus males, only patients with TICI 2b/3 reperfusion were included, for consistency with prior studies.[42]

All *P* values are 2-sided, with values <0.05 defined as statistically significant. SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis.

Results

Among the 542 patients enrolled in the SWIFT, STAR, and SWIFT PRIME studies, 98 patients were excluded because they did not receive EST (SWIFT PRIME), and 55 were excluded because they received EST with an older generation device (SWIFT). Thus, 389 (72%) met inclusion criteria for this study. The cohort consisted of 98 patients from SWIFT PRIME, 202 patients from STAR, and 89 patients from SWIFT. Among this cohort, 214 (55%) were females, and 175 (45%) were males. Average age was 67±13, NIHSS was 17±5, presentation ASPECTS was 8±2, and nearly equal number of patients suffered infarcts of the left hemisphere (48%) compared with the right hemisphere.

As shown in Table 1, there were notable differences in presentation characteristics between females and males. Compared with males, in our cohort, females were ≈5 years older (69 versus 64 years, *P*<0.001) Females were less likely to have a history of smoking (11% versus 28%, *P*<0.0001). In addition, rates of atrial fibrillation and coronary disease/myocardial infarction differed, with females more likely to be diagnosed with atrial fibrillation (45% versus 30%, *P*=0.002) and less likely to be diagnosed with coronary disease (4% versus 9%, *P*=0.03). Importantly, premorbid mRS (32% versus 20%, mRS>0, *P*=0.06), rates of diabetes mellitus (16% versus 18%, *P*=0.79), hyperlipidemia (36% versus 41%, *P*=0.35) and prior stroke (17% versus 14%, *P*=0.58), and hypertension (69% versus 60%, *P*=0.09) were similar. Rates of intravenous thrombolysis were similar between the 2 groups. Also noteworthy were the comparable time intervals for females and males, in terms of time from onset to emergency room presentation (166 versus 165 minutes, *P*=0.96), as well as time from emergency room presentation to groin puncture (89 versus 93 minutes, *P*=0.39) and OTR (294 versus 302 minutes, *P*=0.46).

Treatment and outcomes characteristics for females and males can be found in Table 2. Rates of successful reperfusion (TICI 2b/3) were nearly identical (87% versus 83%, *P*=0.37). Other procedural characteristics including number of Solitaire device passes as well as procedural time (puncture to reperfusion time) were comparable. Radiographic outcomes, however, differed in that more females suffered from hemorrhagic infarction type 1 (10% versus 5%, *P*=0.04), whereas more males suffered from hemorrhagic infarction type 2 (2% versus 9%, *P*=0.003). Despite females presenting at an older age and with higher rates of atrial fibrillation, there were no statistical differences in clinical outcomes at 90 days (mRS 0–2) by sex after adjustment for age, atrial fibrillation, premorbid mRS, and baseline NIHSS using logistic regression (odds ratio, 1.01; 95% CI, 0.64–1.59).

We then further examined factors known to be effect modifiers of clinical outcomes in EST to compare the relationship by sex. As shown in Figure 1A, OTR had a clear effect on outcome, with the likelihood of good neurological outcome diminishing with increased OTR. However, the relationship between OTR and outcome was not different between females and males. In ordinal analysis across the 7-level mRS, the likelihood of shift in mRS at 90 days was 1.2% for females and 1% for males per 5-minute delay in reperfusion (*P*=0.27 for difference between females and males). We then examined the effect of infarct size on clinical outcomes for females versus males. As shown in Table I in the online-only Data Supplement, in trichotomized analysis of ASPECTS from 24-hour CT scan, the likelihoods of good neurological outcome were similar across all 3 levels. As such, the likelihood of good neurological outcome did not differ in females compared with males by final infarct size.

Next, we examined the effect of age on outcome. As shown in Figure 1B, in logistic regression adjusted for baseline NIHSS, target occlusion location, ASPECTS, baseline serum glucose, prestroke mRS, atrial fibrillation, smoking status, and IV-tPA use, the likelihood of a good neurological outcome diminished with increased age. However, there was no statistically significant difference in the likelihood of good neurological outcome with advancing age for females versus males. The degree and quality of angiographic collaterals were similar between males and females. As shown in Table II in the online-only Data Supplement, the rates of excellent collaterals (grade 3–4) were nearly identical between the 2 sexes. Looking at only the subset of patients with TICI 2b/3 reperfusion, collateral grade did not lead to better outcomes in one sex compared with the other.

We then calculated the effect of sex on DALY after EST with successful reperfusion. Because prior studies have demonstrated that differences in stroke outcomes for females compared with males may be a function of age of

Table 1. Patient Demographics by Sex

Characteristic	Males (n=175)	Females (n=214)	*P* Value
Age, y	64±12	69±13	<0.001
NIHSS at baseline	17±5	17±5	0.21
Left-side infarct	75 (44)	107/210 (51)	0.22
Medical history			
Atrial fibrillation	53 (30)	97 (45)	0.002
Hypertension	105 (60)	147 (69)	0.09
CAD/myocardial disease	16 (9)	8 (4)	0.03
Diabetes mellitus	31 (18)	35 (16)	0.79
Hyperlipidemia	72 (41)	78 (36)	0.35
Peripheral artery disease	7 (4)	6 (3)	0.58
Smoking	49/173 (28)	23 (11)	<0.0001
Prior stroke/TIA	25 (14)	36 (17)	0.58
Prestroke mRS			
0	127/158 (80)	129/187 (69)	0.06
1	19/158 (12)	37/187 (20)	0.06
2	8/158 (5)	18/187 (10)	0.06
3	4/158 (3)	2/187 (1)	0.06
4	0/158 (0)	1/187 (1)	0.06
Occlusion location			
ICA	33/166 (20)	38/207 (18)	0.62
M1	106/166 (64)	143/207 (69)	0.62
M2	26/166 (16)	24/207 (12)	0.62
M3	1/166 (1)	2/207 (1)	0.62
ASPECTS at baseline	8±2	8±2	0.24
IV-alteplase	117 (67)	141 (66)	0.91
Baseline glucose	125±49	131±57	0.30
Time intervals, min			
Onset to ER	165±104	166±101	0.96
ER to groin	93±50	89±49	0.39
Onset to groin	254±97	256±90	0.87
Onset to reperfusion	302±95	294±94	0.46

Data are reported as mean±SD or n/N (%). Instances in which data were missing or incompletely captured are represented with the appropriate denominator as above. ASPECTS indicates Alberta Stroke Program Early CT Score; CAD, coronary artery disease; ER, emergency room; ICA, internal carotid artery; IV, intravenous; M, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

Table 2. Procedural Characteristics and Outcomes

Characteristic	Males (n=175)	Females (n=214)	*P* Value
TICI 2b/3	145 (83)	186 (87)	0.37
Passes	2±1	2±1	0.17
Puncture to reperfusion, min	48±34	44±26	0.23
Intracranial hemorrhage			
Any ICH	43 (25)	41 (19)	0.22
HI-1	8 (5)	22 (10)	0.04
HI-2	15 (9)	4 (2)	0.003
PH-1	9 (5)	6 (3)	0.29
PH-2	2 (1)	4 (2)	0.70
Functional independence (mRS 0–2)	98 (56)	114 (53)	0.54
Mortality at 90 days	17 (10)	21 (10)	1.000
mRS			
mRS 0	29 (16)	34 (16)	0.61
mRS 1	40 (23)	54 (25)	0.61
mRS 2	29 (17)	26 (12)	0.61
mRS 3	21 (12)	38 (18)	0.61
mRS 4	29 (16)	37 (17)	0.61
mRS 5	7 (4)	7 (3)	0.61
mRS 6	20 (12)	18 (9)	0.61

Data are reported as mean±SD or N (%). HI,[24] indicates hemorrhagic infarction; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; PH,[24] parenchymal hemorrhage; and TICI, Thrombolysis in Cerebral Infarction.

onset, stroke severity, prestroke function, and presence of atrial fibrillation, these features were included in our model. As shown in Table III in the online-only Data Supplement, in unadjusted analysis, full life expectancy for males was greater than for females by ≈1 year. After adjusting for age of onset of stroke, stroke severity (which was similar between the 2 sexes), prestroke mRS, atrial fibrillation, smoking status, and use of IV-tPA, as shown in Table 3, females experienced better poststroke disability outcomes. Specifically, females were observed to have an 8.9 DALY benefit relative to males, which decreased by 0.1 per year of age at the time of stroke. The mean advantage to females over the entire cohort was 1.8 DALY, after averaging over all ages but still controlling for presentation NIHSS. These findings were similar in our sensitivity analysis, in which an alternative method was used to calculate poststroke life expectancy. As shown in Tables IV and V in the online-only Data Supplement, females in this analysis enjoyed an 11.2 DALY benefit relative to males, with a decrease of 0.13 per year of age at the time of stroke, for a mean advantage to females of 2.2 DALY for the cohort.

Discussion

In this study of almost 400 patients treated with EST, females with large vessel occlusion were older than males, with higher rates of atrial fibrillation. Despite these differences, 90-day clinical outcomes were similar between the sexes after adjustment for age, stroke severity, atrial fibrillation, and prestroke mRS. Age at onset, OTR, ASPECTS, and collateral grade did not have differential effects on outcome after EST in females compared with males. Using published population-level data on poststroke mortality, we found a benefit of ≈2 DALYs after EST in females compared with males across the cohort.

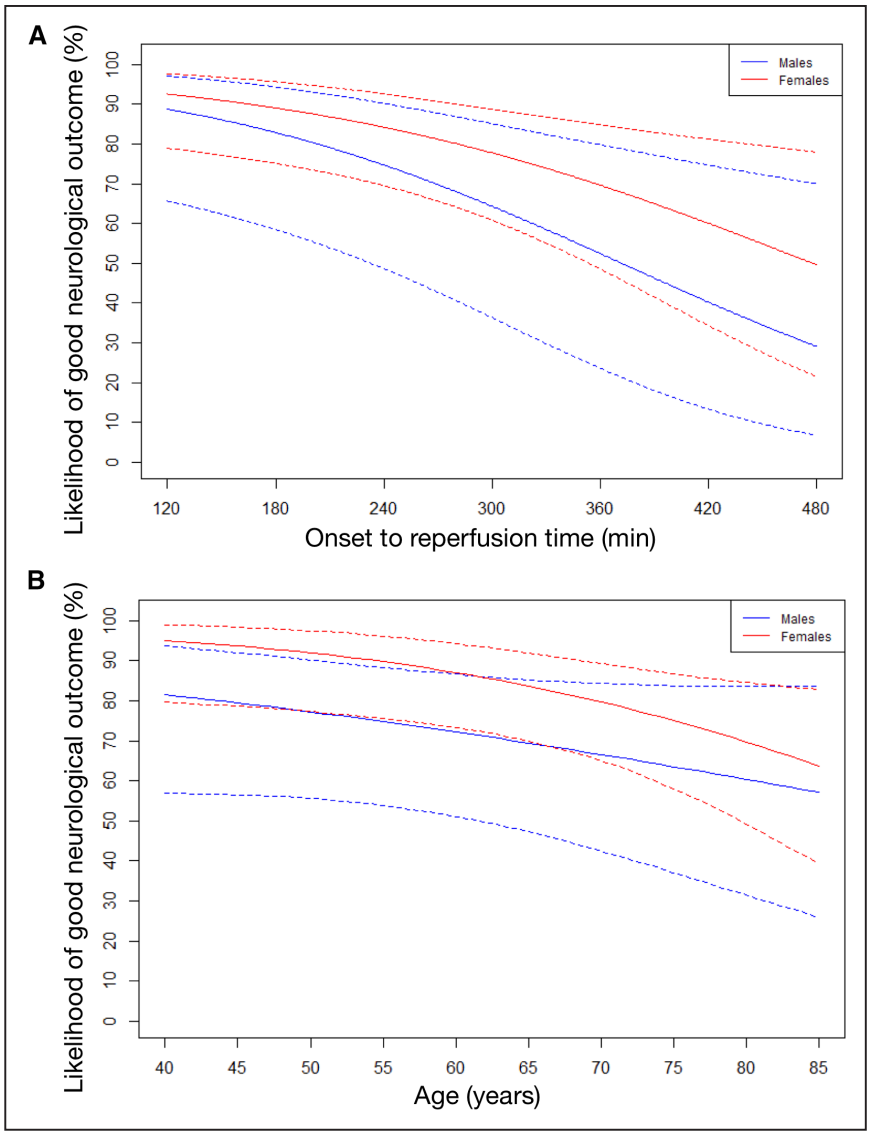

Figure 1. Effect of onset to reperfusion time (OTR) and age on outcomes after endovascular stroke therapy in females and males. Adjusted logistic regressions demonstrating the likelihood of good neurological outcome at 90 d (modified Rankin Scale, 0–2 at 90 d) relative to OTR (**A**) and age (**B**) by sex. Solid line represents point estimates, and dashed lines represent 95% CIs.

Our finding of greater rates of atrial fibrillation and older age are consistent with sex demographic data reported in a number of studies.[13–15] Multiple prior studies have evaluated the differential outcomes for females compared with males after AIS. These results have covered the full range of possibilities, with many suggesting worse outcomes, others neutral and some improved outcomes.[2–8,14] In this study, we sought to assess the effect of sex on outcome in the modern-day era of AIS with EST, as this treatment is associated with a dramatic effect size on patient outcome in appropriately selected patients. As such, prior reports on the influence of sex on stroke outcomes may not apply to patients who receive this treatment.

Studies of the effect of intravenous thrombolysis have shown similar outcomes between females and males at 90 days, whereas in the PROACT-2 study (Pro-Urokinase for Acute Cerebral Thromboembolism-2), intra-arterial thrombolysis resulted in improved outcomes for females relative to males.[7,8] Conversely, in MR CLEAN, EST demonstrated improved 90-day clinical outcomes in males, but not in females relative to medical management alone.[21] This finding, however, was not replicated in a large meta-analysis of multiple EST trials.[18]

In addition, because some of the variability in the reported differences in outcomes for females compared with males with AIS may be secondary to differences in presentation characteristics, we sought to perform a comprehensive analysis of the effect of sex on the association between clinical outcome and factors affecting outcome in EST. The influence of advancing age, greater OTR, and collateral grade have all been well described in large vessel occlusion stroke treated with EST.[34,35,42,43] In our study, we found that these features continued to remain important outcomes predictors; however, there was no effect of sex on the effect of these predictors on outcome.

As has been shown previously, life expectancy and post-stroke life expectancy differ between females and males.[14] As such, 90-day disability outcomes will not accurately represent treatment impact for comparisons by sex. To this end, we determined the effect of EST on optimal life years, by calculating DALYs. This metric, which is widely used in epidemiological studies, provides a continuous metric to measure

Table 3. Disability-Adjusted Life Year Outcomes

Parameter	Change in DALY per Unit of Parameter	SE	*P* Value
Age (linear, per year of age)	−1.5	0.2	<0.0001
Age (quadratic, per year of squared age)	0.007	0.001	<0.0001
NIHSS at baseline (linear, per point)	−1.2	0.3	0.0004
Age by NIHSS interaction (quadratic, per year×point)	0.01	0.005	0.0107
Prestroke mRS (per point)	−1.4	0.4	0.0007
Atrial fibrillation (yes vs no)	0.5	0.6	0.4200
Smoking status (yes vs no)	0.7	0.8	0.3495
IV-tPA administered (yes vs no)	0.05	0.6	0.9288
Female sex (vs male)	8.9	3.1	0.0038
Per year of age, female sex (vs male)	−0.1	0.05	0.0253

DALY indicates disability-adjusted life years; IV-tPA, intravenous tissue-type plasminogen activator; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

years of healthy life lost due to disability and years of life lost due to premature mortality. It has been used previously in AIS treatment studies to demonstrate that treatment with IV-tPA within 3 hours resulted in 4.4 additional years of optimal life.[25] Here, because of the previously described association of age, stroke severity, premorbid mRS, and presence of atrial fibrillation with sex, we adjusted our analysis for these factors and found a relative advantage to females compared with males in optimal life years gained after EST, which diminished with increasing age of onset as shown in Figure 2. Based on our findings, females treated with EST in our cohort enjoyed a DALY advantage over males up to the age of late 80s.

Our study has limitations. The analyses in this work were derived from data from 3 clinical trials with strict selection criteria. As such, these findings should not be generalized to all EST procedures, if performed without the same rigid criteria as may be frequently done in clinical practice (ie, treating patients with advanced age, minor stroke, greater premorbid disability, or less stringent imaging selection criteria). In addition, this analysis combined multiple trials with different inclusion/exclusion criteria. In sensitivity analysis, the largest effect was seen in the STAR trial (Figure I in the online-only Data Supplement), which was also the study that contributed the most patients to the cohort. In addition, our DALY calculation made use of population-level data on poststroke mortality in females versus males. It is possible that this mortality rate may change over time, or other studies will find differing rates. For this reason, we performed an additional, sensitivity analysis with a different methodology, in which we found very similar results.

In this comprehensive assessment of the impact of sex on outcome in EST, we found that sex did not differentially influence the relationship between outcome after EST and OTR, age, ASPECTS, and collateral grade. Despite presentations at an older age, a lower rate of poststroke mortality rate coupled with equivalent adjusted 90-day poststroke disability outcomes resulted in females benefitting from 2 years of greater optimal life compared with males after EST.

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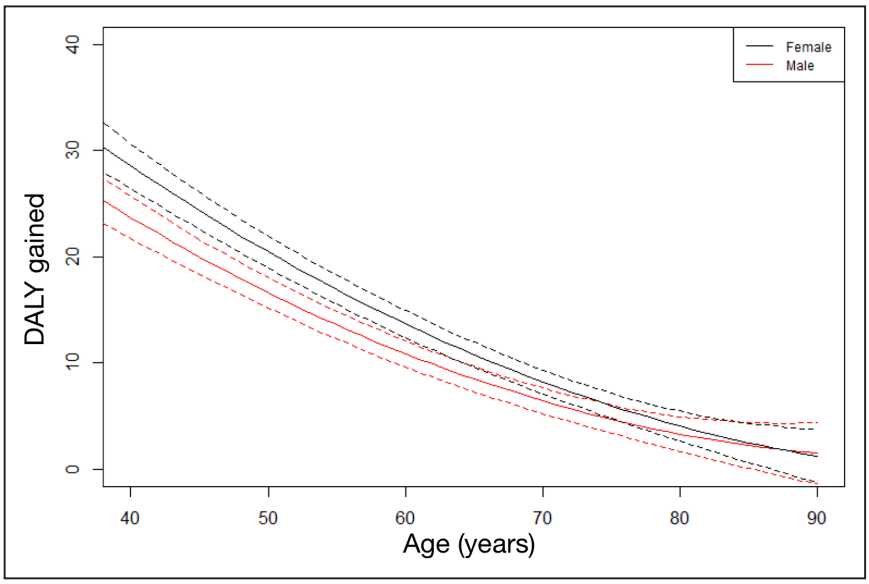

Figure 2. Effect of age on adjusted disability-adjusted life years (DALY) outcomes in females and males. Predicted DALY outcomes adjusted for age and stroke severity after endovascular stroke therapy in females and males by age. Solid line represents point estimates, and dashed lines represent 95% CIs.

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References

1. Persky RW, Turtzo LC, McCullough LD. Stroke in women: disparities and outcomes. *Curr Cardiol Rep.* 2010;12:6–13. doi: 10.1007/s11886-009-0080-2
2. Kent DM, Price LL, Ringleb P, Hill MD, Selker HP. Sex-based differences in response to recombinant tissue plasminogen activator in acute ischemic stroke: a pooled analysis of randomized clinical trials. *Stroke.* 2005;36:62–65. doi: 10.1161/01.STR.0000150515.15576.29
3. Lasek-Bal A, Puz P, Kazibutowska Z. Efficacy and safety assessment of alteplase in the treatment of stroke - gender differences. *Neurol Res.* 2014;36:851–856. doi: 10.1179/1743132814Y.0000000331
4. Savitz SI, Schlaug G, Caplan L, Selim M. Arterial occlusive lesions recanalize more frequently in women than in men after intravenous tissue plasminogen activator administration for acute stroke. *Stroke.* 2005;36:1447–1451. doi: 10.1161/01.STR.0000170647.42126.a8
5. Silva GS, Lima FO, Camargo EC, Smith WS, Lev MH, Harris GJ, et al. Gender differences in outcomes after ischemic stroke: role of ischemic lesion volume and intracranial large-artery occlusion. *Cerebrovasc Dis.* 2010;30:470–475. doi: 10.1159/000317088
6. Meseguer E, Mazighi M, Labreuche J, Arnaiz C, Cabrejo L, Slaoui T, et al. Outcomes of intravenous recombinant tissue plasminogen activator therapy according to gender: a clinical registry study and systematic review. *Stroke.* 2009;40:2104–2110. doi: 10.1161/STROKEAHA.108.546325
7. Hill MD, Kent DM, Hinchey J, Rowley H, Buchan AM, Wechsler LR, et al; PROACT-2 Investigators. Sex-based differences in the effect of intra-arterial treatment of stroke: analysis of the PROACT-2 study. *Stroke.* 2006;37:2322–2325. doi: 10.1161/01.STR.0000237060.21472.47
8. Arnold M, Kappeler L, Nedeltchev K, Brekenfeld C, Fischer U, Keserue B, et al. Recanalization and outcome after intra-arterial thrombolysis in middle cerebral artery and internal carotid artery occlusion: does sex matter? *Stroke.* 2007;38:1281–1285. doi: 10.1161/01.STR.0000259711.13490.23
9. Wyller TB, Sødring KM, Sveen U, Ljunggren AE, Bautz-Holter E. Are there gender differences in functional outcome after stroke? *Clin Rehabil.* 1997;11:171–179. doi: 10.1177/026921559701100211
10. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke.* 2009;40:1082–1090. doi: 10.1161/STROKEAHA.108.540781
11. Lisabeth LD, Reeves MJ, Baek J, Skolarus LE, Brown DL, Zahuranec DB, et al. Factors influencing sex differences in poststroke functional outcome. *Stroke.* 2015;46:860–863. doi: 10.1161/STROKEAHA.114.007985
12. Gall S, Phan H, Madsen TE, Reeves M, Rist P, Jimenez M, et al. Focused update of sex differences in patient reported outcome measures after stroke. *Stroke.* 2018;49:531–535. doi: 10.1161/STROKEAHA.117.018417
13. Turtzo LC, McCullough LD. Sex differences in stroke. *Cerebrovasc Dis.* 2008;26:462–474. doi: 10.1159/000155983
14. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex differences in long-term mortality after stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): a meta-analysis of individual participant data. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003436.
15. Renoux C, Coulombe J, Li L, Ganesh A, Silver L, Rothwell PM. Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke*. 2017;48:2731–2738.
16. de Ridder IR, Fransen PS, Beumer D, Berkhemer OA, van den Berg LA, Wermer MJ, et al. Is intra-arterial treatment for acute ischemic stroke less effective in women than in men? *Interv Neurol.* 2016;5:174–178. doi: 10.1159/000447331
17. Madsen TE, DeCroce-Movson E, Hemendinger M, McTaggart RA, Yaghi S, Cutting S, et al. Sex differences in 90-day outcomes after mechanical thrombectomy for acute ischemic stroke. *J Neurointerv Surg.* 2019;11:221–225. doi: 10.1136/neurintsurg-2018-014050
18. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al; HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
19. Hong KS. Disability-adjusted life years analysis: implications for stroke research. *J Clin Neurol.* 2011;7:109–114. doi: 10.3988/jcn.2011.7.3.109
20. Barker-Collo S, Bennett DA, Krishnamurthi RV, Parmar P, Feigin VL, Naghavi M, et al; GBD 2013 Writing Group; GBD 2013 Stroke Panel Experts Group. Sex differences in stroke incidence, prevalence, mortality and disability-adjusted life years: results from the Global Burden of Disease Study 2013. *Neuroepidemiology.* 2015;45:203–214. doi: 10.1159/000441103
21. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al; SWIFT Trialists. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet.* 2012;380:1241–1249. doi: 10.1016/S0140-6736(12)61384-1
22. Pereira VM, Gralla J, Davalos A, Bonafé A, Castaño C, Chapot R, et al. Prospective, multicenter, single-arm study of mechanical thrombectomy using Solitaire flow restoration in acute ischemic stroke. *Stroke.* 2013;44:2802–2807. doi: 10.1161/STROKEAHA.113.001232
23. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med.* 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
24. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet.* 2007;369:275–282. doi: 10.1016/S0140-6736(07)60149-4
25. Hong KS, Saver JL. Years of disability-adjusted life gained as a result of thrombolytic therapy for acute ischemic stroke. *Stroke.* 2010;41:471–477. doi: 10.1161/STROKEAHA.109.571083
26. Arias E. United States life tables, 2004. *Natl Vital Stat Rep*. 2007;56:1–39.
27. Hong KS, Saver JL. Quantifying the value of stroke disability outcomes: WHO global burden of disease project disability weights for each level of the modified Rankin Scale. *Stroke.* 2009;40:3828–3833. doi: 10.1161/STROKEAHA.109.561365
28. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al; Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet.* 2004;363:1925–1933. doi: 10.1016/S0140-6736(04)16405-2
29. Cabral NL, Gonçalves AR, Longo AL, Moro CH, Costa G, Amaral CH, et al. Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. *J Neurol Neurosurg Psychiatry.* 2009;80:755–761. doi: 10.1136/jnnp.2009.172098
30. Sturm JW, Donnan GA, Dewey HM, Macdonell RA, Gilligan AK, Thrift AG. Determinants of handicap after stroke: the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke.* 2004;35:715–720. doi: 10.1161/01.STR.0000117573.19022.66

31. Anderson CS, Jamrozik KD, Broadhurst RJ, Stewart-Wynne EG. Predicting survival for 1 year among different subtypes of stroke. Results from the Perth Community Stroke Study. *Stroke.* 1994;25:1935–1944.
32. Appelros P, Nydevik I, Seiger A, Terént A. High incidence rates of stroke in Orebro, Sweden: further support for regional incidence differences within Scandinavia. *Cerebrovasc Dis.* 2002;14:161–168. doi: 10.1159/000065680
33. Bejot Y, Catteau A, Caillier M, Rouaud O, Durier J, Marie C, et al. Trends in incidence, risk factors, and survival in symptomatic lacunar stroke in Dijon, France, from 1989 to 2006: a population-based study. *Stroke.* 2008;39:1945–1951. doi: 10.1161/STROKEAHA.107.510933
34. Sheth SA, Jahan R, Gralla J, Pereira VM, Nogueira RG, Levy EI, et al; SWIFT-STAR Trialists. Time to endovascular reperfusion and degree of disability in acute stroke. *Ann Neurol.* 2015;78:584–593. doi: 10.1002/ana.24474
35. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: A Meta-analysis. *JAMA.* 2016;316:1279–1288. doi: 10.1001/jama.2016.13647
36. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet.* 2000;355:1670–1674. doi: 10.1016/s0140-6736(00)02237-6
37. Vemmos KN, Bots ML, Tsibouris PK, Zis VP, Grobbee DE, Stranjalis GS, et al. Stroke incidence and case fatality in southern Greece: the Arcadia stroke registry. *Stroke.* 1999;30:363–370.
38. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. *Stroke.* 2007;38:2906–2911. doi: 10.1161/STROKEAHA.107.484139
39. Smadja D, Cabre P, May F, Fanon JL, René-Corail P, Riocreux C, et al; ERMANCIA Study Group. ERMANCIA: Epidemiology of Stroke in Martinique, French West Indies: part I: methodology, incidence, and 30-day case fatality rate. *Stroke.* 2001;32:2741–2747.
40. Correia M, Silva MR, Matos I, Magalhães R, Lopes JC, Ferro JM, et al. Prospective community-based study of stroke in Northern Portugal: incidence and case fatality in rural and urban populations. *Stroke.* 2004;35:2048–2053. doi: 10.1161/01.STR.0000137606.34301.13
41. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, et al; Auckland Regional Community Stroke Study Group. Ethnic disparities in incidence of stroke subtypes: Auckland Regional Community Stroke Study, 2002-2003. *Lancet Neurol.* 2006;5:130–139. doi: 10.1016/S1474-4422(05)70325-2
42. Sheth SA, Sanossian N, Hao Q, Starkman S, Ali LK, Kim D, et al; UCLA Collateral Investigators. Collateral flow as causative of good outcomes in endovascular stroke therapy. *J Neurointerv Surg.* 2016;8:2–7. doi: 10.1136/neurintsurg-2014-011438
43. Mueller-Kronast NH, Zaidat OO, Froehler MT, Jahan R, Aziz-Sultan MA, Klucznik RP, et al; STRATIS Investigators. Systematic evaluation of patients treated with neurothrombectomy devices for acute ischemic stroke: primary results of the STRATIS registry. *Stroke.* 2017;48:2760–2768. doi: 10.1161/STROKEAHA.117.016456